# EXHIBIT F

# Effectiveness of Glucosamine for Symptoms of Knee Osteoarthritis: Results from an Internet-Based Randomized Double-Blind Controlled Trial

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**PURPOSE:** To present the safety and effectiveness results of a prototypical 12-week, double-blind, randomized placebo-controlled trial of glucosamine among subjects with knee osteoarthritis who were recruited and followed entirely over the Internet.

**METHODS:** The study comprised 205 subjects aged 45 years or older with symptomatic knee osteoarthritis who were recruited over the Internet; eligibility was authenticated through medical record review. Participants were assigned randomly to 1.5 g/d of glucosamine (n = 101) or placebo (n = 104), of whom 108 completed the intervention (93 in each arm). The primary outcome measure was the pain subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (Likert version). Additional outcome measures included the physical function and stiffness subscales and overall score of the questionnaire, and analgesic use.

**RESULTS:** There was no difference between treatment and control groups in terms of change in pain score (2.0 ± 3.4 vs. 2.5 ± 3.8, $P = 0.41$), stiffness (0.7 ± 1.6 vs. 0.8 ± 1.5, $P = 0.52$), physical function (5.2 ± 9.5 vs. 4.6 ± 9.6, $P = 0.49$), overall score (7.8 ± 13.1 vs. 7.8 ± 13.5, $P = 0.81$), and analgesic use (133 ± 553 vs. −88 ± 755, $P = 0.12$). Stratification by osteoarthritis severity, glucosamine product, and use of a nonsteroidal anti-inflammatory drug, as well as exclusion of opiate users, did not alter the results. The number and type of adverse events reported was similar between the groups.

**CONCLUSION:** Our results suggest that although glucosamine appears to be safe, it is no more effective than placebo in treating the symptoms of knee osteoarthritis. **Am J Med. 2004;117:643–649.** ©2004 by Elsevier Inc.

Glucosamine, an amino-monosaccharide component of cartilage, has been promulgated in lay publications as a remedy for osteoarthritis (1), a condition for which there is currently no effective medical remedy. As such, glucosamine is now one of the most frequently used dietary supplements in the United States (2,3). Results from several industry-sponsored trials have suggested the efficacy of glucosamine for osteoarthritis (4–10). Since glucosamine is relatively safe (4), it could have utility even if only modestly efficacious. However, a meta-analysis of early trials revealed methodologic problems and possible publication bias (11), and two recent independent trials failed to demonstrate efficacy (12,13). These studies highlight the complexities associated with testing such products and the need for further research. However, osteoarthritis trials are burdensome and costly, especially in pursuit of modest effect sizes.

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In contemplating these obstacles, we developed a plan for performing clinical trials over the Internet. Our aim was to test the feasibility of online clinical trials by performing a prototypical double-blind, randomized placebo-controlled trial of glucosamine among subjects recruited and followed entirely over the Internet.

## METHODS

We sought to recruit 200 subjects with knee osteoarthritis and to enroll them in a 12-week, double-blind, randomized placebo-controlled trial of glucosamine 1.5 g/d. The entire trial, including recruitment, was performed using the Internet. Methodological observations from this study have already been reported (14). In brief, our goal was to translate as many elements as possible of a traditional, double-blind, randomized placebo-controlled trial into the electronic domain, conducted through a website portal. We constructed a secure website that interfaced with a Microsoft SQL Server (Redmond, Washington) database. The site included a description of the study, the consent form, and an eligibility screen. Two key elements were a batching utility that sent e-mail reminders to participants before scheduled online assessments and a code that presented the questionnaires to each participant when logging onto the website for these assessments. The study was reviewed and approved by the Institutional Review Board at Boston University School of Medicine.



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### Recruitment of Participants and Confirmation of Eligibility

We solicited applicants using advertisements and an interactive eligibility screening form on our website. Applicants who passed the screen were asked to read, print, and send us the consent form and medical record release by mail so that we could obtain their medical records, radiographs, or magnetic resonance imaging (MRI) scans. We imposed inclusion and exclusion criteria using the responses to questions posed over the Internet combined with documentation of knee osteoarthritis from radiographs, MRI scans, or medical reports. Inclusion criteria included age ≥45 years; a signed consent form and permission to obtain medical reports, including radiographic films; self-reported use of analgesics for knee osteoarthritis on most days; at least one knee meeting the clinico-radiologic American College of Rheumatology criteria for knee osteoarthritis (15), determined by an affirmative response to the question "On most days do you have pain, aching, or stiffness in either of your knees?"; and at least one area of tibiofemoral or patellofemoral osteophytosis documented on a radiograph, MRI, or radiologic report. Exclusion criteria included knee injection within 60 days of the baseline online assessment; arthroplasty in the study knee; current use of glucosamine, chondroitin, or agents that claim to possess osteoarthritis structure-modifying properties; participation in other clinical trials or use of experimental agents; and allergy to shrimp or shellfish. Subjects with diabetes or a family history of diabetes were cautioned but not excluded.

### Classification of Severe Knee Osteoarthritis

Severe knee osteoarthritis was classified with an algorithm that used key phrases in the radiological reports that indicated total joint space loss: *severe joint space narrowing*; *complete loss of joint space*; *bone-on-bone*; *marked narrowing*; *obliteration of joint space*; *severe osteoarthritis*; or *advanced osteoarthritis*. We tested the algorithm in 107 participants for whom we had obtained both radiographs and a radiological report. The $\kappa$ value for concordance of any of these phrases in the report with radiographic total joint space loss was 0.93.

### Glucosamine

Glucosamine and placebo capsules were initially purchased from Physiologics (Thornton, Colorado). Laboratory analysis confirmed an average content of 496 mg of glucosamine sulfate per capsule. The placebo capsules were identical in appearance and contained rice starch. During the study, the manufacturer declined to supply more placebo capsules. Subsequent supplies of glucosamine and placebo were obtained from Rotta Pharmaceuticals (Neptune, New Jersey). This formulation consisted of a powder sealed in sachets (glucosamine hydrochloride 1.5 g, which was manufactured to pharmaceutical grade purity, or rice powder). These were identical in appearance and flavor.

### Randomization, Allocation Concealment, and Dosing

Randomization and product labeling were performed by a statistician (ML) and staff otherwise uninvolved with running the trial. They supplied the packages, identified only by a code number on the label, to study personnel. Participants underwent random assignment to treatment or control group upon completion of a 2-week run-in phase, and were sent study materials by express mail at monthly intervals. The switch from the Physiologics to Rotta glucosamine product occurred at enrolment of the 163rd participant. Prior participants took three capsules per day; subsequent enrollees took one sachet of powder per day.

### Outcome Measures

The primary outcome was the pain subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (Likert version), a validated knee osteoarthritis symptom assessment instrument (16,17). This 24-item instrument comprises three subscales (pain, stiffness, and function) and generates scores for each subscale as well as an overall score (range, 0 to 96). Participants answered the full questionnaire at the first, fifth, and seventh online assessments, and the pain subscale at other online assessments. The pain and stiffness subscale questions were posed in a knee-specific fashion and pertained to the study knee.

Prospective information on the daily use of analgesics was also collected using paper calendars sent by mail. These data were used to compute daily analgesic use as acetaminophen equivalents (in mg) averaged over each 4-week period. We used the change in analgesic use between the first and last 4-week period as a secondary outcome.

### Adherence

We asked participants to report the number of study pills or sachets remaining at the end of each month, and to return unused materials by mail. Participants were considered adherent if they took >80% of the assigned medication at these time points.

### Adverse Event Assessment

We prompted participants to report relevant events or adverse experiences at any time using forms on the website or a toll-free telephone line, or by e-mailing the study staff directly.

### Power

Power projections were based on a previous glucosamine trial that provided the Western Ontario and McMaster Universities Osteoarthritis Index scores, and that ob-

served a between-group difference (± SD) in change in pain subscale of 0.95 ± 4.0 (18). Thus, with 100 subjects per arm and a significance of 0.05 (two-sided), we expected 80% power to detect an effect size difference of 0.4 in the pain subscale (19).

### *Statistical Analysis*

Baseline characteristics were compared using chi-squared or *t* tests. Although enrollees were considered to have completed the trial if they had participated for at least 6 weeks (a period in which induction of efficacy would be expected ), we included all randomized enrollees (101 in the glucosamine group; 104 in the placebo group) in the intent-to-treat analyses by carrying the last observation forward. Change in outcome scores and in use of analgesics was calculated by subtracting the last assessment score from the baseline score. Between-group differences were evaluated using *t* tests. Generalized linear models were used to test for differences after adjusting for body mass index, sex, and use of analgesics, and least squares means were used to obtain adjusted means. We also stratified analyses by severity of osteoarthritis, product (Physiologics vs. Rotta), and nonsteroidal anti-inflammatory drug (NSAID) and opiate use. All statistical analyses were conducted with SAS software (Cary, North Carolina); *P* values <0.05 were considered significant.

## RESULTS

Of 293 eligible applicants, 37 participated in website testing and development and 51 declined to participate (Figure 1). The remaining 205 individuals were assigned randomly to the glucosamine (n = 101) or placebo (n = 104) arm. Nineteen enrollees were lost to follow-up, discontinued intervention, or violated protocol prior to week 6, leaving 186 participants (93 in each arm). Duration of participation was similar in the two treatment groups (75% [n = 76] vs. 74% [n = 77] completed the full 12 weeks), while 94% (n = 95) in the glucosamine group and 91% (n = 95) in the placebo group participated for at least 6 weeks. Among the 205 participants, 175 (85%) reported pill counts at either visit 5 or visit 7. Among these, 150 (86%) were at least 80% compliant.

The assignment groups differed in sex (57 % vs. 71% women for glucosamine vs. placebo, $P = 0.04$), NSAID use (74% vs. 87%, $P = 0.03$), and body mass index (31.0 ± 7.6 kg/m$^2$ vs. 34.1 ± 9.0 kg/m$^2$, $P = 0.01$) (Table 1).

### *Osteoarthritis Index Scores and Use of Analgesics*

Pain scores decreased during the course of the trial (Figure 2). However, there were no between-group differences for any of the outcomes either in the intent-to-treat or completers' analyses (Table 2). The between-group difference for mean change was −0.5 (95% confidence interval [CI]: −1.7 to 0.7; $P = 0.41$) for pain and 0.6 (95% CI: −4.0 to 5.2; $P = 0.81$) for overall score. The results were not changed after adjustment for sex, body mass index, and baseline score, or by expression of the outcome as a percentage change. Similarly, the results were consistent when stratified by radiographic severity (mean change in difference in pain score in the severe group = 1.4 [95% CI: −1.3 to 4.1; $P = 0.32$]; nonsevere group = 0.3 [95% CI: −1.0 to 1.6; $P = 0.68$]), by use of NSAIDs (users = 0.52 [95% CI: −0.8 to 1.9; $P = 0.45$]; nonusers = 0.03 [95% CI: −3.1 to 3.2, $P = 0.98$]), or after excluding those who used opiates (0.6; 95% CI: −0.7 to 1.8; $P = 0.36$). A larger mean change in difference in pain score was seen in the Rotta group (2.6; 95% CI: 0.1 to 5.1; $P = 0.05$) than in the Physiologics group (0.2; 95% CI: −1.2 to 1.6; $P = 0.77$), although the results favored placebo.

### *Adverse Events*

Adverse events were similar in the glucosamine (n = 18) and placebo (n = 14) groups. The most frequent reports were of gastrointestinal distress (4 glucosamine, 6 placebo) and arthralgia (5 glucosamine, 2 placebo). Other adverse events in the glucosamine group included dysgeusia (n = 1), sexual dysfunction (n = 1), feet swelling (n = 1), arthralgia (n = 2), central nervous system problems (n = 2), influenza-like symptoms (n = 1), and high blood pressure (1), whereas other adverse events in the placebo group included restless leg syndrome (n = 1), feet swelling (n = 1), central nervous system problems (n = 2), and constipation (n = 1). One participant in the placebo group was hospitalized due to dizziness, nausea, and chest pressure.

## DISCUSSION

We found that glucosamine was no more effective than placebo in treating symptoms of knee osteoarthritis. Our study also demonstrates the feasibility of performing a clinical trial entirely over the Internet. In a previous report (14), we showed that participants in an Internet-based trial were motivated, adherent, and largely similar to participants in traditional clinical trials of knee osteoarthritis, and that the osteoarthritis index scores were similar to those reported in traditional settings (14). Even though we enrolled subjects who were remote from our center, we were able to perform most of the procedures used in a controlled clinical trial, such as allocation concealment, outcome assessment, pill counts, analgesic use counts, and ascertainment of adverse events. We also documented a decrease in pain score that was similar to that often observed in traditional clinical trials, consistent with regression to the mean.

Our findings should be interpreted in light of several unique aspects of the Internet-based design, and in view that this study was performed primarily to test the feasi-

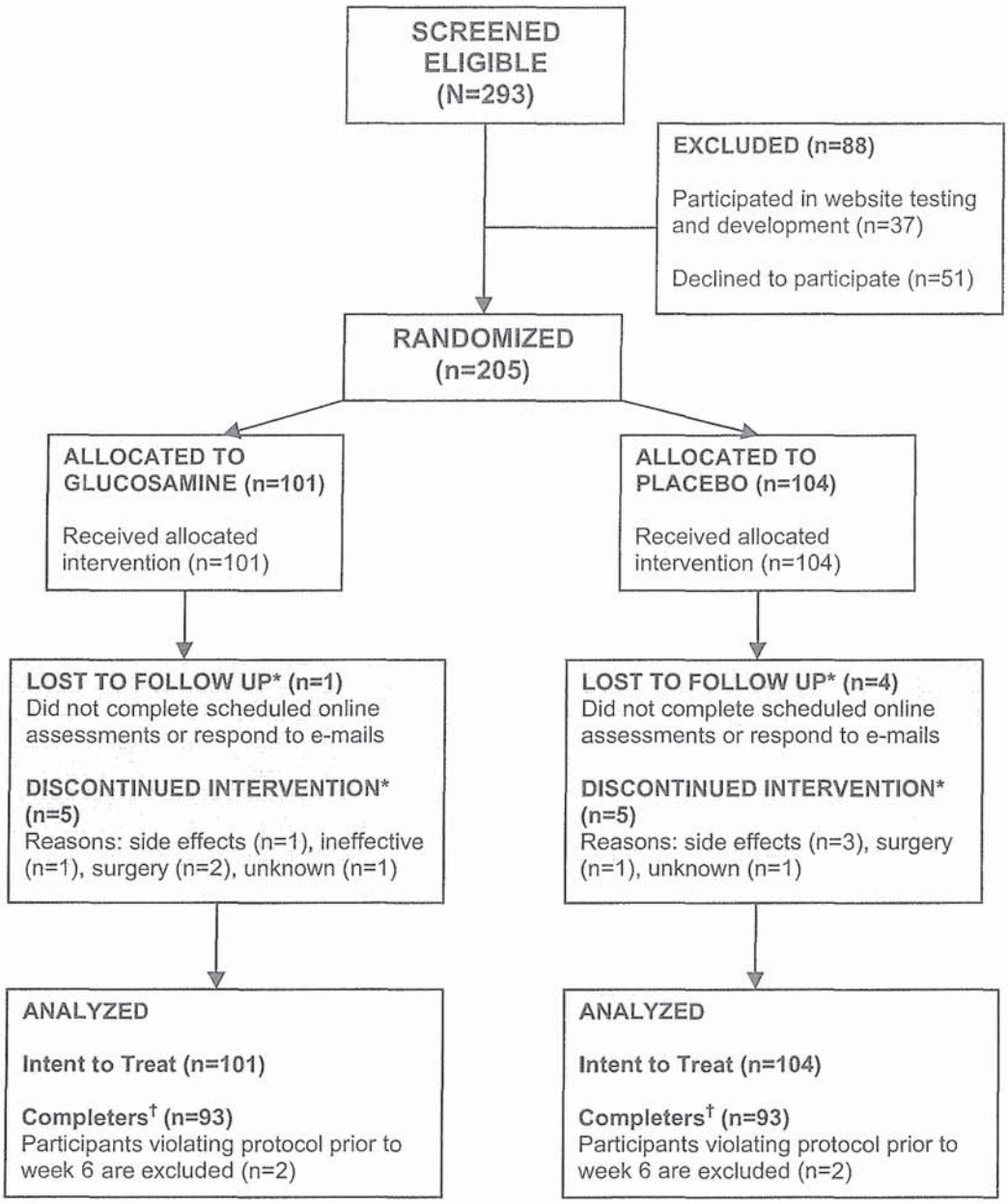


**Figure 1.** Flow diagram of participant progress through phases of the trial. The asterisk (*) indicates prior to week 6. The dagger (†) indicates inclusion of subjects who participated at least through week 6.

bility and methodological aspects of this approach, rather than the efficacy of glucosamine itself. Thus, we set a modest recruitment goal, which limited power to detect small effects. Our trial should be characterized as an effectiveness rather than efficacy study because of the inclusive eligibility criteria and lack of direct observation.

One unanticipated logistical problem was the inability of our primary supplier to provide sufficient placebo capsules for all participants. Since the focus of this endeavor was on the methodology of the Internet-based trial approach, we chose to find a new supplier for the remaining participants, even though there are numerous problems inherent in changing the formulation of the intervention. Ultimately, we found no difference between the glucosamine and placebo groups in any of the outcome measures, at any of the assessment time points. While there could be many reasons for these findings, the most concerning possibility is the lack of validity of the Internet-

**Table 1.** Baseline Characteristics of Participants of an Online Glucosamine Trial, by Treatment Group

| Characteristic | Glucosamine (n = 101) | Placebo (n = 104) | *P* Value |
|---|---|---|---|
| | Number (%) or Mean ± SD | | |
| Age (years)* | | | 0.57 |
| ≤54 | 33 (33) | 33 (32) | |
| 55–64 | 36 (36) | 35 (34) | |
| 65–74 | 27 (27) | 27 (26) | |
| 75–84 | 4 (4) | 9 (9) | |
| 85–94 | — | — | |
| ≥95 | 1 (1) | — | |
| Female sex | 58 (57) | 74 (71) | 0.04 |
| White non-Hispanic | 88 (87) | 94 (90) | 0.62 |
| Income ($) | | | 0.43 |
| ≤34,999 | 24 (24) | 25 (24) | |
| 35,000–54,999 | 9 (9) | 17 (16) | |
| ≥55,000 | 12 (12) | 10 (10) | |
| Undisclosed | 56 (55) | 52 (50) | |
| Retirement status | | | 0.67 |
| Retired | 33 (33) | 38 (37) | |
| Undisclosed | 22 (22) | 25 (24) | |
| Used NSAID | 75 (74) | 90 (87) | 0.03 |
| Severe osteoarthritis† | 83 (82) | 85 (82) | 0.93 |
| Body mass index (kg/m$^2$) | 31.0 ± 7.6 | 34.1 ± 9.0 | 0.01 |

* One 44-year-old subject is included in the 45–54 year age group.
† Severe classification designates total joint space loss.
NSAID = nonsteroidal anti-inflammatory drug.

based approach. This could occur, for example, if the participants provided frivolous responses or were nonadherent to the study medications. However, the Western Ontario and McMaster Universities Osteoarthritis Index is a well-validated instrument that has been tested for use via computer (16,17,20). Indeed, data from psychosocial

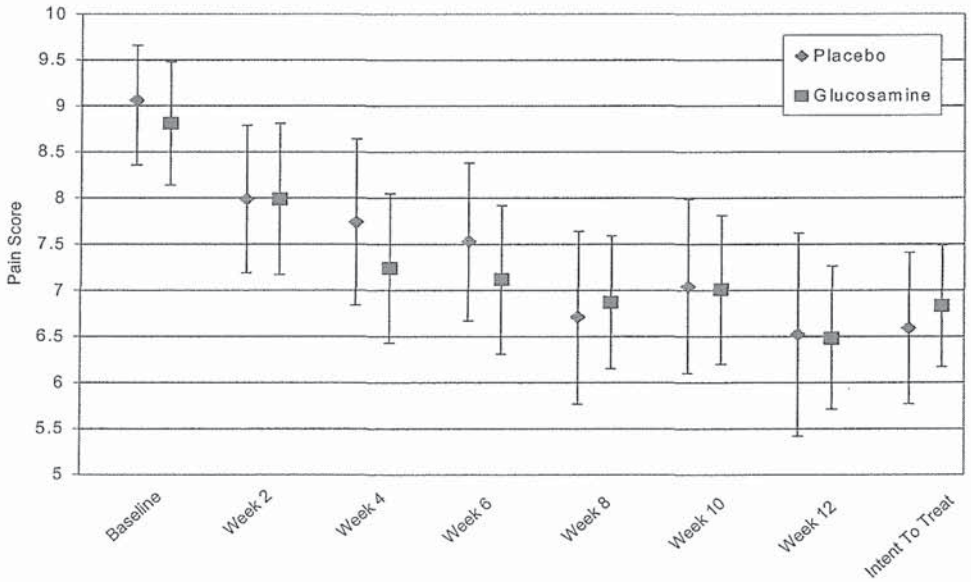


**Figure 2.** Mean pain scores and 95% confidence intervals at online assessment time points throughout the trial. Higher scores indicate more pain. Pain scores did not differ by treatment group at any online assessment or in intent-to-treat analyses.

**Table 2.** Comparison of Unadjusted and Adjusted Change in Outcome Scores and Use of Analgesics, by Treatment Group (Intent-to-Treat Analysis)*

| Outcome | Glucosamine (n = 101) | | Placebo (n = 104) | | Between-Group Difference in Mean Change (95% Confidence Interval)† | *P* Value† |
|---|---|---|---|---|---|---|
| | Mean ± SD | | | | | |
| | Baseline | Change | Baseline | Change | | |
| Pain score | 8.8 ± 3.4 | 2.0 ± 3.4 | 9.1 ± 3.4 | 2.5 ± 3.8 | −0.5 (−1.7 to 0.7) | 0.41 |
| Stiffness score | 4.2 ± 1.5 | 0.7 ± 1.6 | 4.1 ± 1.7 | 0.8 ± 1.5 | −0.2 (−0.7 to 0.3) | 0.52 |
| Physical function score | 30.2 ± 11.2 | 5.2 ± 9.5 | 31.6 ± 12.8 | 4.6 ± 9.6 | 1.2 (−2.1 to 4.5) | 0.49 |
| Total score | 43.2 ± 15.1 | 7.8 ± 13.1 | 44.8 ± 16.9 | 7.8 ± 13.5 | 0.6 (−4.0 to 5.2) | 0.81 |
| Analgesic use‡ (mg) | 1845 ± 2952 | 133 ± 553 | 1309 ± 1476 | −88 ± 755 | 173 (−45 to 391) | 0.12 |

* Higher scores indicate worse pain, stiffness, and physical function.
† Pain, stiffness, physical function, and total scores are adjusted for age, sex, body mass index, baseline analgesic use; analgesic use is adjusted for sex and body mass index.
‡ Expressed as acetaminophen equivalents.

studies indicate that the anonymity afforded by computer-administered questionnaires may enhance the validity of responses (21). Furthermore, the scores generated in our trial are consistent in both value and variability with those in similar traditional trials (14). Information from the pill counts also suggests that our participants were reasonably compliant with the regimen. These factors, together with rigorous authentication, disease confirmation, and the principles of the randomized controlled trial design, suggest that lack of validity is an unlikely explanation for our null result.

Another explanation might be that performance problems prevented us from detecting a true difference. For example, randomization was unbalanced for sex and body mass index. Adjustment for these covariates, however, made no difference to our findings. It is more likely that aspects of the sample characteristics limited effectiveness in the trial. For example, participants tended to be taking NSAIDs or other analgesics, and had more severe disease, as compared with patients in positive glucosamine trials (22). On the other hand, our results remained consistently negative after stratification for NSAID use, opiate use, and radiographic severity. Another possibility is that the product tested was not efficacious. There has been conjecture that the varying formulations of glucosamine products might influence efficacy (23). In this respect, it might have been informative to compare results among participants in the two glucosamine product groups, but numbers in the later (Rotta) glucosamine group were too small to draw meaningful inferences.

Lastly, change in analgesic use over the course of the trial could have masked a beneficial effect of glucosamine. We observed an increase in analgesic use in the glucosamine group and a slight decrease in use in the placebo group. However, this difference represents a minimal amount of acetaminophen and is unlikely to explain the null finding in this trial.

We embarked on this study against a background of numerous positive industry-funded glucosamine trials (11). Since then, however, three independently funded traditional clinical trials have been published (13,24,25), all with null outcomes. While our results are consistent with those of these trials, methodologic issues and sample differences among these trials indicate that further studies will be needed to resolve the issue of the effectiveness of glucosamine products. The Internet-based clinical trial approach may be an effective way to perform such studies quickly and efficiently.

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